and specific nickel compounds - nickel carbonyl and nickel subsulfide - have been evaluated. Summaries of these evaluations are on IRIS.

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

__III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Nickel, soluble salts
CASRN -- 7440-02-0

Not available at this time.

__III.B. OTHER ASSESSMENTS

Substance Name -- Nickel, soluble salts
CASRN -- 7440-02-0

Content to be determined.

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Nickel, soluble salts
CASRN -- 7440-02-0
Last Revised -- 06/01/90

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

<<< Nickel, soluble salts >>>

__IV.A. CLEAN AIR ACT (CAA)

No data available

----------<<< Nickel, soluble salts >>>----------

__IV.B. SAFE DRINKING WATER ACT (SDWA)

No data available

----------<<< Nickel, soluble salts >>>----------

__IV.C. CLEAN WATER ACT (CWA)

No data available

----------<<< Nickel, soluble salts >>>----------

__IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

No data available

----------<<< Nickel, soluble salts >>>----------

__IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

----------<<< Nickel, soluble salts >>>----------

__IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

___IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

----------<<< Nickel, soluble salts >>>----------

__IV.G. SUPERFUND (CERCLA)

No data available

V. SUPPLEMENTARY DATA

Substance Name -- Nickel, soluble salts
CASRN -- 7440-02-0
Last Revised -- 09/30/87

The information contained in this section (subsections A and B) has been extracted from the EPA Chemical Profiles Database, which has been compiled from a number of secondary sources and has not undergone formal Agency review. The complete reference listings for the citations in this section are provided in Service Code 5. The user is urged to read Background Document 5 in Service Code 5 for further information on the sources and limitations of the data presented here.

<<< Nickel, soluble salts >>>

V.A. ACUTE HEALTH HAZARD INFORMATION

Toxicity -- Numerous cases of dermatitis have been reported (Clayton and Clayton, 1981-82).

Medical Conditions Generally Aggravated by Exposure -- Not Found

Signs and Symptoms of Exposure -- Symptoms include nausea, vomiting, diarrhea, central nervous system depression (Weiss, 1980, p. 1105), coughing, shortness of breath, chest pain, fever and weakness upon inhalation (Rumack, 1975 to Present).

----------<<< Nickel, soluble salts >>>----------

V.B. PHYSICAL-CHEMICAL PROPERTIES

Chemical Formula -- Ni

Molecular Weight -- 58.70

Boiling Point -- 5139F, 2837C (Merck, 1983)

Specific Gravity (H2O=1) -- 8.90 (Sax, 1979)

Vapor Pressure (mmHg) -- 1 at 1810C (Sax, 1979)

Melting Point -- 2831F, 1555C (Merck, 1983)

Vapor Density (AIR=1) -- Not Found

Evaporation Rate (Butyl acetate=1) -- Not Found

Solubility in Water -- Insoluble (Weast, 1979)

Flash Point (Method Used) -- Not Found

Flammable Limits -- Not Found

Appearance and Odor -- Silvery metal (Weast, 1979); lustrous white metal (Merck, 1983)

Conditions or Materials to Avoid -- Finely divided nickel (e.g. Raney nickel catalysts) may become hot enough to ignite if exposed to air or moisture (Student, 1981, p. 363). Materials containing potassium perchlorate with nickel and titanium powders and infusional earth give severe explosions during a friction test. Dioxane reacts explosively with hydrogen and Raney nickel above 210C (NFPA, 1978). Also, aluminum; aluminum trichloride; ethylene; hydrogen; methanol; non-metals; oxidants; sulfur compounds (Sax, 1984, p. 1990), and selenium metal (Weiss, 1980, p. 1105) are incompatible with nickel.

Hazardous Decomposition or Byproducts -- Not Found

Use -- Nickel is used in nickel-plating; for various alloys such as new silver, Chinese silver, and German silver; for coins, electrotypes, lighting-rod tips, electrical contacts and electrodes, spark plugs, machinery parts; as a catalyst for hydrogenation of organic substances; in manufacturing of Monel metal, stainless steels, and nickel-chrome resistance wire; and in alloys for electronic and space applications (Merck, 1983).

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_VI. BIBLIOGRAPHY

Substance Name -- Nickel, soluble salts
CASRN -- 7440-02-0
Last Revised -- 04/01/90

__VI.A. ORAL RfD REFERENCES

Ambrose, A.M., D.S. Larson, J.R. Borzelleca and G.R. Hennigar, Jr. 1976. Long-term toxicologic assessment of nickel in rats and dogs. J. Food Sci. Technol. 13: 181-187.

Edwards, M.J. 1986. Hyperthermia as a teratogen: A review of experimental studies and their clinical significance. Teratogen. Carcinogen. Mutagen. 6: 563-582.

RTI (Research Triangle Institute). 1986. Two-generation reproduction and fertility study of nickel chloride administered to CD rats in drinking water. Interim report: Ninety day toxicity study of nickel chloride administered to CD rats in drinking water. Report submitted to Office of Solid Waste, U.S. Environmental Protection Agency, Washington, DC.

RTI (Research Triangle Institute). 1987. Two-generation reproduction and fertility study of nickel chloride administered to CD rats in drinking water. Report submitted to Office of Solid Waste, U.S. Environmental Protection Agency, Washington, DC.

Schroeder, H.A. and M. Mitchener. 1971. Toxic effects of trace elements on the reproduction of mice and rats. Arch. Environ. Health. 23: 102.

U.S. EPA. 1983. Health Assessment Document for Nickel. Prepared by the Office of Health and Envioronmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC. (External Review Draft)

U.S. EPA 1985. Drinking Water Criteria Document for Nickel. Quantification of Toxicological Effects chapter only. Prepared by the Office of Health and

Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC.

U.S. EPA. 1986. A 90 day gavage study on Albino rats using nickel. Submitted by American Biogenics Corp. Decatur, IL.

----------<<< Nickel, soluble salts >>>----------

__VI.B. INHALATION RfD REFERENCES

None

----------<<< Nickel, soluble salts >>>----------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

None

----------<<< Nickel, soluble salts >>>----------

__VI.D. DRINKING WATER HA REFERENCES

None

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SYNONYMS

Substance Name -- Nickel, soluble salts
CASRN -- 7440-02-0
Last Revised -- 09/30/87

7440-02-0
C.I. 77775
NICHEL
Nickel
Nickel, soluble salts

Selenium and Compounds; CASRN 7782-49-2 (06/01/91)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR Selenium and Compounds

File On-Line 03/01/91

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	06/01/91
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	06/01/91
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	no data	
Supplementary Data (V.)	no data	

I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Selenium and Compounds
CASRN -- 7782-49-2
Last Revised -- 06/01/91

The Reference Dose (RfD) is based on the assumption that thresholds exist for

certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file when a review of that evaluation is completed.

<<< Selenium and Compounds >>>

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Clinical selenosis	NOAEL: 0.015 mg/kg/day	3	1	5E-3 mg/kg/day
Human Epidemiological Study	LOAEL: 0.023 mg/kg/day			
Yang et al., 1989b				

*Conversion Factors: NOAEL (0.853 mg/day) and LOAEL (1.261 mg/day) calculated from regression analysis (log Y = 0.7671log X - 2.248, where Y = blood selenium and X = selenium intake) as detailed in Yang et al. (1989a) based upon the correlation (r = 0.962) between dietary selenium intake and blood selenium level for data showing incidence of clinical selenosis in adults based on an average adult body weight of 55 kg (Yang et al., 1989b).

<<< Selenium and Compounds >>>

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Yang, G., S. Yin, R. Zhou, et al. 1989b. Studies of safe maximal daily dietary Se-intake in a seleniferous area in China. II. Relation between Se-intake and the manifestation of clinical signs and certain biochemical alterations in blood and urine. J. Trace Elem. Electrolytes Health Dis. 3(2): 123-130.

Yang et al. (1989b), in a follow-up to an earlier study (Yang et al., 1983), studied a population of approximately 400 individuals living in an area of China with unusually high environmental concentrations of selenium (Se). The subjects were evaluated for clinical and biochemical signs of Se intoxication. Three geographical areas with low, medium and high selenium levels in the soil and food supply were chosen for comparison in the studies. The earlier Yang et al. (1983) study was conducted in response to endemic selenium intoxication in two separate areas with sample sizes of only 6 and 3. Comparisons were then made to a selenium-adequate area (n=8) and low- selenium area (n=13). The Yang et al. (1989a,b) studies provide a much larger sample size and include additional analysis of tissue selenium levels. This allows a more accurate estimation of the dose-response relationship observed for selenium toxicity. Selenium levels in soil and approximately 30 typical food types commonly eaten by the exposed population showed a positive correlation with blood and tissue Se levels. The daily average Se intakes, based on lifetime exposure, 70, 195 and 1438 ug for adult males and 62, 198 and 1238 ug for adult females in the low-, medium- and high-selenium areas, respectively.

Significant correlations demonstrated between Se concentrations of various tissues were used to estimate the minimal daily Se intake values that elicited various alterations in biochemical parameters indicative of possible Se-induced liver dysfunction (i.e., prolongation of clotting time and serum glutathione titer) and clinical signs of selenosis (i.e., hair or nail loss, morphological changes of the nails, etc.). In this manner, a marginal safe level of daily Se intake was estimated.

Analysis of the results indicated that perisistent clinical signs of selenosis were observed only in 5/439 adults, a potentially sensitive subpopulation. The blood selenium concentration in this group ranged from 1.054 to 1.854 mg/L with a mean of 1.346 mg/L. Clinical signs observed included the characteristic "garlic odor" of excess selenium excretion in the breath and urine, thickened and brittle nails, hair and nail loss, lowered hemoglobin levels, mottled teeth, skin lesions and CNS abnormalities (peripheral anesthesia, acroparesthesia and pain in the extremities). Alterations in the measured biochemical parameters occurred at dietary intake levels of 750-850 ug/day. These alterations were described as a delay in 2'prothrombin time, i.e., increase in blood coagulation time and reduction in blood glutathione concentration. However, these indicators were poorly characterized and are not typically used as an index for clinical selenosis resulting from chronic exposure to selenium (NAS, 1989). Based upon the blood selenium levels shown to reflect clinical signs of selenium intoxication, a whole blood selenium concentration of 1.35 mg/L corresponding to 1.261 mg of daily selenium intake is indicative of the lowest correlative selenium intake causing overt signs of selenosis. The next lowest whole blood selenium concentration of 1.0 mg/L, corresponding to 0.853 mg selenium/day, produces no clinical signs of selenosis. The NOAEL for this study is 0.85 mg Se/day and the LOAEL is 1.26 mg Se/day.

A group of 142 volunteers in South Dakota and Wyoming were recruited by Longnecker et al. (1991) at random from households listed in a telephone directory or from ranches with suspected high selenium intake based on previous cases of livestock selenosis. The geographical areas were chosen because of known seleniferous topsoil and high concentrations of selenium in plants and food. The subjects were followed for 1 year and completed health questionnaires, underwent physical examinations, provided blood samples for clinical assessment, and provided blood, urine, toenails and duplicate-plate food collections for selenium analysis. The average selenium intake was 239 ug/day, approximately 2-3 times higher than the national average. The concentration of selenium in whole blood, serum, urine and toenails and the amount in diet were highly correlated. Blood selenium concentration was highly correlated with selenium intake. The correlation was very similar to that reported by Yang et al. (1989a). Liver function (prothrombin time and alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase and alkaline phosphatase), hematologic functon (leukocyte count, hemoglobin and hematocrit) and clinical chemistry (sodium, potassium and chloride concentration) were not found to be altered as a result of selenium intake. High regression coefficient predictor variables for selenium toxicity (muscle twitching, paresthesia, nail loss, nail lines, hair loss and garlic breath) were not found in increased frequency for this population. No signs of selenium toxicity were found in this population, including individuals whose selenium intake was as high as 724 ug/day. This report corroborates that of Yang et al. (1989b), which showed that a selenium intake of up to 853 ug/day is not associated with characteristic nail or hair loss typical of selenium intoxication.

<<< Selenium and Compounds >>>

I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 3. An uncertainty factor of 3 was applied to the NOAEL to account for sensitive individuals. A full factor of 10 was not deemed necessary since a moderately-sized human population was exposed to high levels of selenium throughout a lifetime, the essential requirement for selenium, and because of the purported beneficial anticarcinogenic attributes of excess selenium in the diet.

MF = 1.

<<< Selenium and Compounds >>>

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

The essentiality for selenium has been well-documented in livestock based upon the alleviation of specific deficiency conditions by selenium supplementation of the diet (Combs and Combs, 1986). Selenium has been clearly demonstrated to be a cofactor of glutathione peroxidase, a hydrogen and lipid peroxide reducing enzyme and is therefore essential (Rotruck et al., 1973). Human requirements for selenium were not conclusively established until 1979 when an association was made between low selenium status and cardiomyopathy (Keshan disease) in China for young children and women of child-bearing age (Keshan Disease Research Group, 1979a,b). More recently, iatrogenic episodes of selenium deficiency have been reported in patients receiving intravenous total parenteral administration of feeding solutions devoid of selenium. Symptoms included low glutathione peroxidase activity and low selenium levels in erythrocytes (Levander and Burk, 1986), muscular weakness and discomfort (van Rij et al., 1979) and cardiomyopathy (Johnson et al., 1981). It is important to note that glutathione peroxidase activity is a valid indicator of human selenium status only in populations with relatively low selenium intakes, since the enzyme activity plateaus at adequate selenium intake levels (Whanger et al., 1988), thereby precluding the use of this biochemical indicator under excessive selenium intake situations.

The NAS (1989) has determined the recommended dietary allowance for selenium to be 0.87 ug/kg, or approximately 70 and 55 ug/day for the reference adult North American male and female, respectively. Requirements for selenium increase during pregnancy to 65 ug/day and for lactation to 75 ug/day. Selenium requirements for infants and children vary according to age. However, based on the reference weights of NHANES II, these populations demonstrate an increased requirement per unit weight relative to adults. For infants, the selenium requirement is 1.67 ug/kg and for children the requirement ranges from 1.07-1.53 ug/kg. It should be noted that the most recent RDA for selenium did not consider the 1989 results of Yang et al. (1989a,b) discussed above, but an earlier preliminary report by the same authors (Yang et al., 1983).

Yang et al. (1983) reported clinical signs of selenosis (i.e., loss of hair and nails) in approximately 50% of a population of 248 inhabitants living in Enshi County, Hubei Province of the People's Republic of China. Selenosis was reported in the highest selenium contaminated area where the average daily Se intake was 5.0 mg/day (range 3.2-6.7), but no selenosis occurred when the average intake was 0.750 mg/day (range 0.240-1.51). These estimates, however, were based upon estimates of intake from only 6 and 3 inhabitants in the high and low contaminated areas, respectively. Yang et al. (1989b) reported prolonged clotting time and serum glutathione and these biochemical changes were indicated as adverse effects of selenium exposure. Glutathione is a strong nucleophile that reacts well with soft electrophiles and is an important conjugate-forming compound for the detoxification and excretion of electrophilic metabolites and metabolically produced oxidizing agents. If

The first animal experiment which demonstrated anticarcinogenic effects of selenium was performed by Clayton and Baumann (1949). An approximate 50% reduction in dimethylaminoazobenzene-induced tumor incidence occurred in rats fed a diet supplemented with 5 ppm Se as selenite. Additional evidence subsequently reported, further illustrated the inhibitory effect of selenium on transplantable tumors in rats (Weisberger and Suhrland, 1956a) and leukemia in humans (Weisberger and Suhrland, 1956b). The National Cancer Institute sponsored an extensive study on selenium toxicity in rats in order to resolve the issue of selenium carcinogenicity. Diets containing up to 8 ppm selenium did not increase tumor incidence (Tinsley et al., 1967; Harr et al., 1967). Since 1970, there has been an increased interest in characterizing the anti-carcinogenic and anti-tumorigenic properties of selenium. The number of reports characterizing these properties are too numerous to discuss in detail here. The reader is referred to a review by Milner and Fico (1987) for a more comprehensive treatment of the data base.

The essentiality and toxicity of selenium varies according to the valence state of selenium when incorporated into biomolecules and the form in which selenium is fed or administered. This is especially true when comparing the LD50 value as an index of toxicity for the various selenium compounds. Although it is difficult to make an assessment for several selenium compounds by a similar mode of administration in a common species, there is general agreement that sodium selenite, sodium selenate, selenomethionine and selenoglutathione are among the more toxic species (Combs and Combs, 1986). The relative potency of systemic toxicity for selenium compounds is also similar in experiments examining potency of anti-tumorigenic activity. In vitro examination of potency of effect of selenium compounds on incubated Ehrlich ascites tumor cells (EATC) showed that sodium selenite is more efficacious in significantly reducing EATC viability than an equivalent concentration of sodium selenate. Although selenium dioxide, selenomethionine and selenocystine ultimately decreased viability of the EATC, nearly 50% more incubation time was required for the same effect (Poirier and Milner, 1979). The same authors investigated the relative potency of various selenium compounds administered intraperitoneally on EATC growth in vivo. Sodium selenite and selenodiglutathione (an intermediate of selenium metabolism) were the most effective forms of selenium in preventing EATC propagation. Sodium selenide, dimethyl selenide and selenocystine were not effective in inhibiting EATC growth (Poirier and Milner, 1983). Similar relative potency results have been reported in in vitro systems for canine mammary cells (Fico et al., 1986) and human mammary cells (Watrach et al., 1984).

Since selenium has been reported to cause growth retardation, decreased fertility, embryotoxicity, fetotoxicity and teratogenic effects in animals, Yang et al. (1989b) made the following observations: Malformation in chickens hatched from locally produced eggs did occur; however, teratogeneic effects in human infants were never seen in this area although Se has been reported to be transmitted through the placenta to the fetus in animals. These findings confirm those reported by Yang et al. (1983) in which chicken eggs from this same area were reported to have very low hatchability and some deformed embryos in those that did hatch.

The developmental toxicity of selenomethionine was investigated by Tarantal et al. (1991) in non-human primates. Forty pregnant long-tailed macaques were dosed daily by nasogastric intubation with 0, 0.025, 0.150 or 0.3 mg selenium/kg as selenomethionine through gestational days 20-50. Dams were examined clinically and the pregnancies of two to three dams within each test group were followed to term (gestational day 165). All other dams were hysterectomized on gestational day 100. Neonates delivered at term were examined for morphometric, neurologic, behavioral and ophthalmologic effects

on days 1, 8, 15, 22 and 30. Pregnancy loss among treated animals was not significantly different from concurrent or historical controls. No statistically significant treatment-related effects were observed at necropsy on gestational day 100. There were no significant maternal or fetal developmental effects or teratogenesis found up to 0.3 mg/kg selenium, the highest dose tested.

Halverson et al. (1966) fed 60-70 g male, post-weanling Sprague-Dawley rats selenium as selenite or seleniferous wheat ad libitum at 1.6, 3.2, 4.8, 6.4, 8.0, 9.6 or 11.2 ppm of selenium (13, 27, 40, 67, 81 or 94 ug/kg/day, respectively). Levels of selenium up to 4.8 ppm showed no effect. At 8.0 ppm selenium as seleniferous wheat, there was an observed decrease in liver weight, increase in spleen weight, and decrease in hemoglobin. Mortality was observed in the groups fed 8.0, 9.6 and 11.2 ppm selenium as seleniferous wheat at incidences of 1/8, 5/8 and 8/8, respectively. The incidences of mortality reported for groups fed 8.0 and 9.6 ppm selenium as selenite were 1/8 and 1/10, respectively. A significant growth reduction was reported for both selenium sources at 6.4 ppm and higher, although feed utilization was not decreased. No other effects were reported for the rats fed sodium selenite.

Schroeder and Mitchener (1971) administered 3 ppm selenium as selenate (390 ug/kg/day) to CD mice through four generations. Maternal effects were not observed. There was a significant increase in young deaths in the F1 generation and an increase in numbers of runts in generations F1 through F3. By the F3 generation there was also a decrease in breeding events.

Rosenfeld and Beath (1954) administered selenium as potassium selenate to sires and pregnant rats through five breeding cycles at 1.5, 2.5 or 7.5 ppm selenium (75, 125 or 375 ug/kg/day). No effect was observed on reproduction, the number of young reared or on the reproduction of two successive generations of dams and sires in groups receiving 1.5 ppm selenium. In the group receiving 2.5 ppm selenium, the was a 50% reduction in the number of young reared. At 7.5 ppm there was a decrease in fertility of the females but not males, a decrease in the number of survivors and a reduction in the rate of growth in the young.

Nobunaga et al. (1979) administered 3 or 6 ppm selenium (390 or 780 ug/kg/day, respectively) as selenite to IVCS mice for 30 days prior to mating and throughout gestation. On day 18 of gestation, maternal mice were sacrificed and the embryos removed. Number of litters, total implants, total implants per dam, dead fetuses, dead embryos, resorptions, surviving fetuses (% to total implants), litter size, gross malformations and skeletal anomalies were not significantly different for either selenium-treated or control mice. The only significant effect noted was a decrease in the body weight of surviving fetuses in mice given 6 ppm selenium.

<<< Selenium and Compounds >>>

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: Medium
Data Base: High
RfD: Medium

Confidence in the chosen principal study is medium. Although this is a human epidemiological study in which a sizable population with sensitive subpopulations was studied, there are still several possible interactions that were not fully accounted for, e.g., fluoride intake and protein status. Also, except for clinical signs of selenosis there are no other reliable indicators, biochemical or clinical, of selenium toxicity. Confidence in the data base is

high because many animal studies and epidemiologic studies (reviewed by Combs and Combs, 1986) support the principal study. Medium to high confidence in the RfD is selected based upon the critical study and RfD levels of confidence.

<<< Selenium and Compounds >>>

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Source Document -- This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation -- U.S. EPA, 1985

Agency Work Group Review: 01/20/88, 03/22/89, 09/21/89, 11/14/90, 03/27/91

Verification Date: 03/27/91

____I.A.7. EPA CONTACTS (ORAL RfD)

Kenneth A. Poirier / ORD -- (513)569-7531 / FTS 684-7531

Gary L. Foureman / ORD -- (919)541-1183 / FTS 629-1183

___I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Selenium and Compounds
CASRN -- 7782-49-2

Not available at this time.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Selenium and Compounds
CASRN -- 7782-49-2
Last Revised -- 06/01/91

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. Background Document 2

(Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Selenium and Compounds >>>

NOTE: This assessment is for the following compounds: Selenium (CASRN 7782-49-2); sodium selenate (CASRN 13410-01-0); sodium selenite (CASRN 10102-18-8); selenious acid (CASRN 7783-00-8); selenic acid (CASRN 7783-08-6); sodium selenide (CASRN 1313-85-5).

II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- D; not classifiable as to carcinogenicity in humans

Basis -- Based on inadequate human data and inadequate evidence of carcinogenicity in animals. The evidence for various selenium compounds in animal and mutagenicity studies is conflicting and difficult to interpret; however, evidence for selenium sulfide is sufficient for a B2 (probable human carcinogen) classification.

<<< Selenium and Compounds >>>

II.A.2. HUMAN CARCINOGENICITY DATA

Inadequate. Data on the potential carcinogenicity of selenium and various selenium compounds in humans are inadequate. Epidemiological studies have evaluated selenium in blood and cancer death rates in areas of high vs. low naturally-occurring selenium. However, these studies have limited value because they do not assess specific selenium compounds or correlate exposure with cancer risk.

Several investigators have studied the association between serum selenium and the risk of cancer through prospective, case-control and nested case-control studies. Analysis of blood serum levels indicated that patients with cancer, particularly gastrointestinal cancer, prostatic cancer, or Hodgkin's lymphoma, had significantly lower blood selenium levels in blood than healthy patients (Shamberger et al., 1973; Salonen et al., 1984; Kok et al., 1987; Willet et al., 1983; Willet and Stampfer, 1986). The risk of cancer for men (Kok et al., 1987) or for all subjects (Willet et al., 1983) in the lowest quintile of serum selenium was twice that of subjects with higher levels.

Geographic correlational studies have compared cancer mortality in areas of high vs. low levels of naturally-occurring selenium. In an ecological study Shamberger and Frost (1969) reported that an inverse relationship existed between cancer death rates and the selenium concentrations in foliage plants of several Canadian provinces. The human cancer death rate in provinces with selenium-containing plants was 122.2 +/- 7.8 (presumably per 100,000 population although this was not specified), while in the provinces devoid of these plants, the human death rate was 139.9 +/- 4.0.

In an ecological study Shamberger and Willis (1971) reported that there was a correlation between decreased cancer death rates in humans and an increase in the selenium in the forage crops in California. In high-selenium areas (selenium 0.11 ppm of forage crops) the cancer death rate per 100,000 was 141.2. In the medium-selenium areas (0.05-0.10 ppm) the cancer death rate

was 190.1. In low-selenium areas (0.02-0.05 ppm) the cancer death rate was 233.0. Shamberger and Willis (1971) also investigated the ratio of observed to expected cancer death rates by anatomic site for men in 17 paired cities including high- and low-selenium areas. The anatomic sites that would come into contact with dietary selenium, such as pharynx, esophagus, stomach, bladder and intestine, showed a substantially lower rate ratio in the high-selenium cities than in the low-selenium cities. Other ecological and prospective studies have correlated an increased incidence of colon, breast and other forms of cancer in humans in geographic areas where selenium is deficient and a lowered cancer incidence with higher selenium concentrations (Schrauzer and Ishmael, 1974; Shamberger, 1976; Schrauzer et al., 1976; Jansson et al., 1978; Yang et al., 1983).

In a study of approximately 300 employees exposed to selenium (form not specified) in a rectifier (electronics) process over a 26-year period, only 17 deaths occurred, 6 of which were because of cancer (Glover, 1970). This number, however, is not statistically different from the 5.1 deaths expected based on national mortality rates. The source of the mortality rates was not specified. Several toxic effects including pulmonary irritation, epigastric pain and dermal irritation and dermatitis were associated with selenium exposure in men, but no carcinogenic effect was reported.

<<< Selenium and Compounds >>>

___II.A.3. ANIMAL CARCINOGENICITY DATA

Inadequate. The carcinogenicity of selenium compounds has been evaluated in several animal studies. However, the data are conflicting and difficult to interpret because of apparent anticarcinogenic activity and high toxicity of some selenium salts. In addition, comparison of the available data is difficult because several different salts with varying degrees of bioavailability were used in the assays.

In a 2-year dietary study reported by Nelson et al. (1943), Osborne-Mendel rats (sex not specified) were fed selenium in the form of seleniferous corn or wheat or ammonium potassium selenide at 5-10 ppm. Survival was lower in the treated rats; 53/126 (42%) rats fed selenium survived 18 months or longer compared with 14/18 (78%) control rats. Of the 53 surviving selenium-treated rats, 43 (81%) developed liver cirrhosis and 11 (21%) developed hepatocellular adenoma or carcinoma. All 11 animals with tumors also had liver cirrhosis. None of the 14 control animals surviving 2 years developed liver tumors. Only pooled group data were reported and no statistical analysis was reported.

No tumors developed in a total of 1437 Wistar rats fed sodium selenite or sodium selenate in the diet at levels of 0.5-16 ppm for their lifetime (Harr et al., 1967; Tinsley et al., 1967). Nonneoplastic liver effects such as hyperemia, cellular degeneration, binucleation, and mild proliferation of hepatocytes were observed at concentrations of 4 ppm and higher.

Long-Evans rats (approximately 50/sex/group at study initiation) received 2 ppm (as selenium) sodium selenate or sodium selenite in drinking water for 1 year, then 3 ppm for the remainder of the study (Schroeder and Mitchener, 1971). The treatment of the control group was not discussed. The animals were observed for the duration of their natural lifespan, approximately 36 months, although one selenate-treated female lived for 5 years. Selenite produced 50% mortality in males by 58 days. At this time, 2 ppm selenate was substituted for selenite in the male group. The concentration of selenium was raised to 3 ppm in this group when the animals were 1 year old; however, the high mortality rendered the group size too small for further statistical analysis. Selenite produced 50% mortality in females by 348 days; selenite-

treated females were sacrificed at 23 months due to high mortality. Selenate produced 50% mortality in females by 1014 days and in males by 962 days. In the control groups 50% mortality was achieved by 872 and 853 days in females and males, respectively. Survival of rats receiving selenate was comparable to controls and median lifespan was increased by >100 days. Body weights of treated males were comparable to controls throughout the study. Body weights of females fed selenate were significantly greater than controls at 24 and 36 months; body weights of females fed selenite were significantly less than controls at all times but 18 months.

Incidence of all tumors and of malignant tumors was significantly increased in the selenate-treated rats compared with the controls. Incidence of all tumors in controls, selenate- and selenite-treated rats was 20/65 (30.8%), 30/48 (62.5%) and 4/32 (12.5%), respectively. Incidence of malignant tumors in the same groups was 11/65 (16.9%), 20/48 (41.7%) and 4/32 (12.5%), respectively. The earliest tumor occurred on day 833 in the control males, on day 633 in the control females, on day 344 in selenate males and on day 633 in selenate females. The shortened survival time of the selenite groups was thought to be responsible for the small number of tumors. This study is considered inadequate because only the heart, lung, liver, kidney and spleen tissues from animals necropsied were examined histologically, and an increase in longevity was observed in selenate-treated female rats.

Schroeder and Mitchener (1972) administered 3 ppm sodium selenate or sodium selenite in drinking water to Swiss mice (50/sex/group). Body weights of selenate-treated animals were comparable to controls. Body weights of males fed selenite were significantly increased compared with controls, but body weights of females fed selenite were significantly decreased compared with controls. Longevity in males fed selenate was increased compared with controls. Longevity in females fed selenate increased, but longevity in females fed selenite decreased compared with controls. When compared to controls, there was no significant increase in total tumor incidence or malignant tumor incidence observed in selenium- (form not specified) treated mice. In the control group 23/119 (19%) had tumors (10/119 (8%) malignant tumors). Selenium-fed mice showed 13/88 (15%) tumors (all were malignant). In selenium-treated group 8/13 malignancies were lymphoma or leukemia, 4/13 were papillary or alveologenic adenocarcinoma and 1/13 an osteosarcoma. In the control group there were two incidences of lymphoma or leukemia, 7 of lung carcinoma and 1 carcinoma of unknown origin. The 13 benign tumors included breast and ovary tumors.

<<< Selenium and Compounds >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Selenium is an essential micronutrient for several species, including humans, and is part of several enzymes such as glutathione peroxidase, an enzyme involved in cellular defense against oxidative damage, and heme oxidase. While low doses of selenium are essential, high doses of selenium or a deficiency of dietary selenium may cause a toxic response. Additionally, selenium may be protective against tumor development. The greatest daily exposure to selenium is via food. Bioavailability of selenium is dependent on numerous factors, including the intake levels, chemical form and nutritional status. Organic forms of selenium are more bioavailable than inorganic forms; selenates and selenites are the inorganic forms more readily absorbed. Sodium selenate and selenite are soluble in water, but the extent to which they are absorbed dermally or through the gastrointestinal tract has not been fully elucidated (U.S. EPA, 1989).

Shamberger (1985) reported that the oral administration of 0.1-6 ppm or

dermal application of 0.005% of selenium reduced incidences of skin, liver, tracheal, intestinal and lung tumors induced by several carcinogens in rats, mice and hamsters. Shamberger theorized that selenium may reduce cellular damage caused by peroxidation of fat. In another study, natural killer (NK) cell activity was significantly increased in female rats administered 0.5 or 2.0 ppm selenium (sodium selenate) in the drinking water for 10 weeks (Koller et al., 1986), suggesting to the authors that NK-sensitive tumors may be prevented by using selenium therapy.

Data on the mutagenicity of selenium and its compounds are equivocal. Selenate and selenite (12 uM) were mutagenic in a reverse mutation assay using Salmonella typhimurium strains TA98, TA100 and TA1537 (Noda et al., 1979) in the absence of rat hepatic homogenates. In a second assay, sodium selenate, but not sodium selenite, was mutagenic; the S. typhimurium strains used were not reported (Lofroth and Ames, 1978). Selenite (selenious acid and sodium selenite) produced DNA damage in Bacillus subtilis strains 17A and 45T; however, selenate (selenic acid and sodium selenate) was negative in the Rec assay (Nakamuro et al., 1976).

Sodium selenide, sodium selenite, and sodium selenate (in order of decreasing activity) caused an increase in unscheduled DNA synthesis in the presence or absence of glutathione in Chinese hamster ovary cells at concentrations of 1.0E-4 M (Whiting et al., 1980). Increased chromosomal aberrations were also produced by sodium selenite at E-5 M in rat lymphocytes (Newton and Lilly, 1986) and by sodium selenite, selenious acid, selenic acid, and selenium oxide at 2.6E-6 M in human lymphocytes (Nakamuro et al., 1976). Sodium selenite produced an increase in chromosomal aberrations in the bone marrow of rats administered a total of 10-12 mg/kg intravenously (near-lethal doses) (Newton and Lilly, 1986). Selenium (elemental), selenium dioxide, sodium selenide, and sodium selenite (in order of decreasing activity) induced an increase in SCEs in human whole-blood cultures; sodium selenate was not mutagenic in this assay (Ray and Altenburg, 1980).

----------<<< Selenium and Compounds >>>----------

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

None.

----------<<< Selenium and Compounds >>>----------

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

None.

----------<<< Selenium and Compounds >>>----------

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1980. Ambient Water Quality Criteria for Selenium. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and

Assessment Office, Cincinnati, OH for the Office of Water Quality Planning and Standards, Washington, DC. EPA 440/5-80-070. NTIS PB 81-117814.

U.S. EPA. 1984. Health Effects Assessment for Selenium (and Compounds). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Emergency and Remedial Response, Washington, DC. EPA/540/1-86-058. NTIS PB 86-134699.

U.S. EPA. 1989. Health and Environmental Effects Document for Selenium and Compounds. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

<<< Selenium and Compounds >>>

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The 1989 Health and Environmental Effects Document on Selenium and Compounds has received OHEA review.

Agency Work Group Review: 11/09/89, 03/07/90

Verification Date: 03/07/90

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

James Cogliano / ORD -- (202)382-2575 / FTS 382-2575

William E. Pepelko / ORD -- (202)382-3903 / FTS 382-3903

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

__III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Selenium and Compounds
CASRN -- 7782-49-2

Not available at this time.

__III.B. OTHER ASSESSMENTS

Substance Name -- Selenium and Compounds
CASRN -- 7782-49-2

Content to be determined.

_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Selenium and Compounds
CASRN -- 7782-49-2

Not available at this time.

_V. SUPPLEMENTARY DATA

Substance Name -- Selenium and Compounds
CASRN -- 7782-49-2

Not available at this time.

_VI. BIBLIOGRAPHY

Substance Name -- Selenium and Compounds
CASRN -- 7782-49-2
Last Revised -- 06/01/91

__VI.A. ORAL RfD REFERENCES

Clayton, C.C. and C.A. Baumann. 1949. Diet and azo dye tumors: Effect of diet during a period when the dye is not fed. Cancer Res. 9: 575-582.

Combs, G.F. and S.B. Combs. 1986. Effects of Selenium Excesses, Chapter 11. In: The Role of Selenium in Nutrition. Academic Press, New York. p. 463-525.

Fico, M.E., K.A. Poirier, A.M. Watrach, M.A. Watrach and J.A. Milner. 1986. Differential effects of selenium on normal and neoplastic canine mammary cells. Cancer Res. 46: 3384-3388.

Francke, K.W. and A.L. Moxon. 1936. A comparison of the minimum fatal doses of selenium, tellurium, arsenic and vanadium. J. Pharmacol. Exp. Ther. 58: 454-459.

Halverson, A.W., I.S. Palmer and P.L. Guss. 1966. Toxicity of selenium to post-weanling rats. Toxicol. Appl. Pharmacol. 9: 477-484.

Harr, J.R. and O.H. Muth. 1972. Selenium poisoning in domestic animals and its relationship to man. Clin. Toxicol. 5(2): 175-186.

Harr, J.R., J.F. Bone, I.J. Tinsley, P.H. Weswig and R.S. Yamamoto. 1967. Selenium toxicity in rats. II. Histopathology. In: Selenium in Biomedicine, O.H. Muth, Ed. AVI, Westport, CT. p. 153-178.

Johnson, R.A., S.S. Baker, J.T. Fallon, et al. 1981. An occidental case of cardiomyopathy and selenium deficiency. N. Engl. J. Med. 304(20): 1210-1212.

Keshan Disease Research Group of the Chinese Academy of Medical Sciences. 1979a. Observations on effect of sodium selenite in prevention of Keshan disease. Chin. Med. J. 92(7): 471-476.

Keshan Disease Research Group of the Chinese Academy of Medical Sciences. 1979b. Epidemiologic studies on the etiologic relationship of selenium and Keshan disease. Chin. Med. J. 92(7): 477-482.

Ketterer, B., B. Coles and D.J. Meyer. 1983. The role of glutathione in detoxication. Environ. Health Perspect. 49: 59-69.

Levander, O.A. and R.F. Burk. 1986. Report on the 1986 A.S.P.E.N. Research Workshop on Selenium in Clinical Nutrition. J. Parenter. Enteral Nutr. 10(6): 545-549.

Longnecker, M.P., P.R. Taylor, O.A. Levander et al. 1991. Selenium in diet, blood, and toenails in relation to human health in a seleniferous area. Am. J. Clin. Nutr. 53: 1288-1294.

Milner, J.A. and M.E. Fico. 1987. Selenium and tumorigenesis. In: Selenium in Biology and Medicine: Proceedings of the Third International Symposium on Selenium in Biology and Medicine, G.F. Combs Jr., J.E. Spallholz, O.A. Levander and J.E. Oldfield, Ed. Van Nostrand Reinhold, New York. p. 1034-1043.

NAS (National Academy of Sciences). 1989. Recommended Dietary Allowances, 10th ed. National Academy Press, Washington, DC. p. 217-224.

Nelson, A.A., O.G. Fitzhugh and H.O. Calvery. 1943. Liver tumors following cirrhosis caused by selenium in rats. Cancer Res. 3: 230-236.

Nobunaga, T., H. Satoh and T. Suzuki. 1979. Effects of sodium selenite on methylmercury embryotoxicity and teratogenicity in mice. Toxicol. Appl. Pharmacol. 47(1): 79-88.

Poirier, K.A. and J.A. Milner. 1979. The effect of various seleno- compounds on Ehrlich ascites tumor cells. Biol. Trace Elem. Res. 1: 25-34.

Poirier, K.A. and J.A. Milner. 1983. Factors influencing the antitumorigenic properties of selenium in mice. J. Nutr. 113: 2147-2154.

Rosenfeld, I. and O.A. Beath. 1954. Effect of selenium on reproduction in rats. Proc. Soc. Exp. Biol. Med. 87: 295-297.

Rosenfeld, I. and O.A. Beath. 1964. Selenium: Geobotany, Biochemistry, Toxicity and Nutrution. Academic Press, New York. p. 198-208.

Rotruck, J.T., A.L. Pope, H.E. Ganther, A.B. Swanson, D.G. Hafeman and W.G. Hoekstra. 1973. Selenium: Biochemical role as a component of glutathione peroxidase. Science. 179: 588-590.

Schroeder, H.A. and M. Mitchener. 1971. Toxic effects of trace elements on the reproduction of mice and rats. Arch. Environ. Health. 23(2): 102-107.

Seifter, J., W.E. Ehrich, G. Hudyma and G. Mueller. 1946. Thyroid adenomas in rats receiving selenium. Science. 103(2687): 762.

Tarantal, A.F., C.C. Willhite, B.L. Lasley et al. 1991. Developmental toxicity of L-selenomethionine in Macaca fascicularis. Fund. Appl. Toxicol. 16: 147-160.

Tinsley, I.J., J.R. Harr, J.F. Bone, P.H. Weswig and R.S. Yamamoto. 1967. Selenium toxicity in rats. I. Growth and longevity. In: Selenium in Biomedicine, O.H. Muth, Ed. AVI, Westport, CT. p. 141-152.

U.S. EPA. 1985. Health Effects Assessment for Selenium (and Compounds). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC. NTIS PB-86-134699/AS.

van Rij, A.M., C.D. Thomson, J.M. McKenzie and M.F. Robinson. 1979. Selenium deficiency in total parenteral nutrition. Am. J. Clin. Nutr. 32: 2076-2085.

Watrach, A.M., J.A. Milner, M.A. Watrach and K.A. Poirier. 1984. Inhibition of human breast cancer cells by selenium. Cancer Lett. 25: 41-47.

Weisberger, A.S. and L.G. Suhrland. 1956a. Studies on analogues of L-cysteine and L-cystine. II. The effect of selenium cystine on Murphy lymphosarcoma tumor cells in the rat. Blood. 11: 11-18.

Weisberger, A.S. and L.G. Suhrland. 1956b. Studies on analogues of L-cysteine and L-cystine. III. The effect of selenium cystine on leukemia. Blood. 11: 19-30.

Whanger, P.D., M.A. Beilstein, C.D. Thomson, M.F. Robinson and M. Howe. 1988. Blood selenium and glutathione peroxidase activity of populations in New Zealand, Oregon and South Dakota. FASEB J. 2(14): 2996-3002.

Yang, G., S. Wang, R. Zhou and S. Sun. 1983. Endemic selenium intoxication of humans in China. Am. J. Clin. Nutr. 37: 872-881.

Yang, G., R. Zhou, S. Yin, et al. 1989a. Studies of safe maximal daily dietary selenium intake in a seleniferous area in China. I. Selenium intake and tissue levels of the inhabitants. J. Trace Elem. Electrolytes Health Dis. 3(2): 77-87.

Yang, G., S. Yin, R. Zhou, et al. 1989b. Studies of safe maximal daily dietary Se-intake in a seleniferous area in China. II. Relation between Se-intake and the manifestation of clinical signs and certain biochemical alterations in blood and urine. J. Trace Elem. Electrolytes Health Dis. 3(2): 123-130.

----------<<< Selenium and Compounds >>>----------

__VI.B. INHALATION RfC REFERENCES

None

----------<<< Selenium and Compounds >>>----------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Glover, J.R. 1970. Selenium and its industrial toxicology. Ind. Med. Surg. 39(1): 26-30.

Harr, J.R., J.F. Bone, I.J. Tinsley, P.H. Weswig and R.S. Yamamoto. 1967. Selenium toxicity in rats. II. Histopathology. In: Selenium in Biomedicine, O.H. Muth, J.E. Oldfield, P.H. Weswig, Ed. Proc. 1st Int. Symp., Oregon State University, 1966. AVI Publishing Co., Westport, Conn. p. 153-178. (Cited in U.S. EPA, 1989)

Jansson, B., M.M. Jacobs and A.C. Griffin. 1978. Gastrointestinal cancer: Epidemiology and experimental studies. Adv. Exp. Med. Biol. 91: 305-322.

Kok, F.J., A.M. De Bruijn, A. Hofman, R. Vermeeren and H.A. Valkenburg. 1987. Is serum selenium a risk factor for cancer in men only? Am. J. Epidemiol. 125(1): 12-16.

Koller, L.D., J.H. Exon, P.A. Talcott, C.A. Osborne and G.M. Henningsen. 1986. Immune responses in rats supplemented with selenium. Clin. Exp. Immunol. 63: 570-576.

Lofroth, G. and B.N. Ames. 1978. Mutagenicity of inorganic compounds in Salmonella typhimurium: Arsenic, chromium and selenium. Mutat. Res. 53: 65-66.

Nakamuro, K., K. Yoshikawa, Y. Sayato, H. Kurata, M. Tonomura and A. Tonomura. 1976. Studies on selenium-related compounds. V. Cytogenetic effect and reactivity with DNA. Mutat. Res. 40: 177-184.

Nelson, A.A., O.G. Fitzhugh and H.O. Calvery. 1943. Liver tumors following cirrhosis caused by selenium in rats. Cancer Res. 3: 230-236. (Cited in U.S. EPA, 1989)

Newton, M.F. and L.J. Lilly. 1986. Tissue-specific clastogenic effects of chromium and selenium salts in vivo. Mutat. Res. 169: 61-69.

Noda, M., T. Takano and H. Sakurai. 1979. Mutagenic activity of selenium compounds. Mutat. Res. 66: 175-179.

Ray, J.H. and L.C. Altenburg. 1980. Dependence of the sister-chromatid exchange-inducing abilities of inorganic selenium compounds on the valence state of selenium. Mutat. Res. 78: 261-266.

Salonen, J.T., G. Alfthan, J.K. Huttunen and P. Puska. 1984. Association between serum selenium and the risk of cancer. Am. J. Epidemiol. 120(3): 342-349. (Cited in U.S. EPA, 1989)

Schrauzer, G.N. and D. Ishmael. 1974. Effects of selenium and of arsenic on the genesis of spontaneous mammary tumors in inbred C3H mice. Ann. Clin. Lab. Sci. 4: 441-447.

Schrauzer, G.N., D.A. White and C.J. Schneider. 1976. Inhibition of the genesis of spontaneous mammary tumors in C3H mice: Effect of selenium and of selenium-antagonistic elements and their possible role in human breast cancer. Bioinorg. Chem. 6: 265-270.

Schroeder, H.A. and M. Mitchener. 1971. Selenium and tellurium in rats: Effect on growth, survival and tumors. J. Nutr. 101: 1531-1540.

Schroeder, H.A. and M. Mitchener. 1972. Selenium and tellurium in mice: Effects on growth, survival and tumors. Arch. Environ. Health. 24: 66-71.

Shamberger, R.J. 1976. Selenium in health and disease. Proceedings of the Symposium on Selenium-Tellurium in the Environment. Industrial Health Foundation, Inc., Pittsburgh, PA. p. 253-267.

Shamberger, R.J. 1985. The genotoxicity of selenium. Mutat. Res. 154: 29-48. (Cited in U.S. EPA, 1989)

Shamberger, R.J. and D.V. Frost. 1969. Possible protective effect of selenium against human cancer. Can. Med. Assoc. J. 100: 682.

Shamberger, R.J. and C.E. Willis. 1971. Selenium distribution and human cancer mortality. Crit. Rev. Clin. Lab. Sci. 2: 211-221.

Shamberger, R.J., E. Rukovena, A.K. Longfield et al. 1973. Antioxidants and cancer. I. Selenium in the blood of normals and cancer patients. J. Natl. Cancer Inst. 50(4): 863-870.

Tinsley, I.J., J.R. Harr, J.F. Bone, P.H. Weswig and R.S. Yamamoto. 1967. Selenium toxicity in rats. I. Growth and longevity. In: Selenium in Biomedicine, O.H. Muth, J.E. Oldfield, P.H. Weswig, Ed. Proc. 1st Int. Symp., Oregon State University, 1966. AVI Publishing Co., Westport, Conn. p. 141-152. (Cited in U.S. EPA, 1989)

U.S. EPA. 1980. Ambient Water Quality Criteria for Selenium. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Quality Planning and Standards, Washington, DC. EPA 440/5-80-070. NTIS PB 81-117814.

U.S. EPA. 1984. Health Effects Assessment for Selenium (and Compounds). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Emergency and Remedial Response, Washington, DC. EPA/540/1-86-058. NTIS PB 86-134699.

U.S. EPA. 1989. Health and Environmental Effects Document for Selenium and Compounds. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

Whiting, R.F., L. Wei and H.F. Stich. 1980. Unscheduled DNA synthesis and chromosome aberrations induced by inorganic and organic selenium compounds in the presence of glutathione. Mutat. Res. 78: 159-169.

Willett, W.C. and M.J. Stampfer. 1986. Selenium and human cancer. Acta Pharmacol. Toxicol. Suppl. 59: 240-247.

Willett, W.C., B.F. Polk, J.S. Morris et al. 1983. Prediagnostic serum selenium and risk of cancer. Lancet. 2: 130-134.

Yang, G., S. Wang, R. Zhou and S. Sun. 1983. Endemic selenium intoxication of humans in China. Am. J. Clin. Nutr. 37: 872-881.

None

SYNONYMS

Substance Name -- Selenium and Compounds
CASRN -- 7782-49-2
Last Revised -- 03/01/91

7782-49-2
Selenium
C.I. 77805
Caswell No. 732
ELEMENTAL SELENIUM
EPA Pesticide Chemical Code 072001
HSDB 4493
SELEN [Polish]
Selenio [Spanish]
Selenium
SELENIUM ALLOY
SELENIUM BASE
SELENIUM DUST
SELENIUM ELEMENTAL
SELENIUM HOMOPOLYMER
UN 2658
13410-01-0
Selenic acid, disodium salt
Caswell No. 791
Disodium selenate
EPA Pesticide Chemical Code 072002
Natriumseleniat [German]
NSC 378348
Selenic acid, disodium salt
Sodium selenate
10102-18-8
Selenious acid, disodium salt
DISODIUM SELENITE
DISODIUM SELENIUM TRIOXIDE
HSDB 768
Natriumselenit [German]
SELENIOUS ACID, DISODIUM SALT
SODIUM SELENITE
UN 2630
7783-00-8
Selenious acid
HSDB 6065
MONOHYDRATED SELENIUM DIOXIDE
Selenious Acid
7783-08-6
Selenic acid
Acide selenique [French]
Acido selenico [Spanish]
HSDB 675
Selenic acid
UN 1905

1313-85-5
Sodium selenide [Na2Se]
Disodium monoselenide
Sodium selenide

Silver; CASRN 7440-22-4 (03/01/91)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR Silver

File On-Line 01/31/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	03/01/91
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	06/01/89
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	on-line	03/01/88
Supplementary Data (V.)	no data	

I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Silver
CASRN -- 7440-22-4
Last Revised -- 03/01/91

The Reference Dose (RfD) is based on the assumption that thresholds exist for

certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file when a review of that evaluation is completed.

<<< Silver >>>

NOTE: The Oral RfD for Silver may change in the near future pending the outcome of a further review now being conducted by the RfD/RfC Work Group.

____I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Argyria	NOAEL: None	2	1	3E-3 mg/kg/day
1-3 Year Therapeutic Treatments in Humans				
Gaul and Staud, 1935	LOAEL: 1.0 g (total i.v. dose)			
Blumberg and Carey, 1934	LOAEL: 6.4 g (total oral dose)			
East et al., 1980	LOAEL: 7.2 g (total oral dose estimated)			
	Average dose = 0.0052 mg/kg/day			

*Conversion Factors:
1000 mg x 1/0.18 x 1/70 kg x 1/25,500 days = 0.0031 mg/kg day;
6400 mg/32.7 kg/25,500 days = 0.0077 mg/kg/day;
7200 mg/58.6 kg/25,500 days = 0.0048 mg/kg/day;
Average = 0.0052 mg/kg/day

<<< Silver >>>

____I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Gaul, L.E. and A.N. Staud. 1935. Clinical spectroscopy. Seventy cases of generalized argyria following organic and colloidal silver medication. J. Am. Med. Assoc. 104: 1387-1390.

Blumberg, H. and T.N. Carey. 1934. Argyremia: Detection of unsuspected and obscure argyria by the spectrographic demonstration of high blood silver. J. Am. Med. Assoc. 103: 1521-1524.

East, B.W., K. Boddy, E.D. Williams, D. MacIntyre and A.L.C. McLay. 1980. Silver retention, total body silver and tissue silver concentrations in argyria associated with exposure to an anti-smoking remedy containing silver

acetate. Clin. Exp. Dermatol. 5: 305-311.

In Gaul and Staud (1935), the LOAEL of 1.0 g was representative of the lowest total doses (0.9-1.5 g) of silver associated with argyria in humans. The doses were administered i.v. over a 2- to 3-year period as silver arsphenamine. No body weight data were reported.

Blumberg and Carey (1934) estimated the total dose from a dosing schedule for silver nitrate taken orally for 1 year as 6.4 g. The subject was an emaciated adult female (32.7 kg).

East et al. (1980) estimated the total body content of silver in one individual with argyria to be 6.4 (plus or minus 2) g. The subject ingested an unknown quantity of silver acetate over a period of 2.5 years. Symptoms of argyria appeared after the first 6 months of exposure. This subject retained 18% of a single dose of orally-administered silver in a separate 30-week experiment. Body weight was given as 58.6 kg.

Argyria is considered adverse beyond its cosmetic effect since it is irreversible and can be clinically mistaken for cyanosis.

Total dose is the most appropriate parameter because argyria is a cumulative effect of silver. The i.v. to oral conversion factor of 1/0.18 is based on the East et al. (1980) retention study. Pharmacokinetic studies in animals suggest that this value (18%) is high and should be considered a conservative estimate. Human body weight defaults to 70 kg in the absence of reported values. The total body burden of silver reported in East et al. (1980) was adjusted for the time of onset of argyria and then converted to an oral dose in the following manner:

6.4 g x 6 months/30 months = 1.3 g body burden; 1.3 g/0.18 = 7.2 g.

<<< Silver >>>

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 2. The standard UF of 10 for the intraspecies (human) variability is not considered appropriate because the affected subjects are of generally poor health and are considered to be sensitive elements of the population. A UF of 2 is used for the LOAEL because the critical effect is considered to be minimally severe.

MF = 1

<<< Silver >>>

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

The supporting animal data suggest that the RfD based on the human data should not be lower.

<<< Silver >>>

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: Medium
Data Base: Medium
RfD: Medium

The human studies rate a medium confidence; they are reasonably good, with

some quantitative dosing data. The data base confidence is medium because the existing animal studies quantitatively support the RfD. Medium confidence in the RfD follows.

<<< Silver >>>

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

U.S. EPA. 1985. Drinking Water Criteria Document for Silver. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. (External Review Draft)

The 1985 Office of Drinking Water document has received Agency review and has been reviewed by several outside experts.

Agency Work Group Review: 10/09/85, 02/05/86

Verification Date: 10/09/85

___I.A.7. EPA CONTACTS (ORAL RfD)

Julie Du / ODW -- (202)382-7583 / FTS 382-7583

Michael L. Dourson / ORD -- (513)569-7573 / FTS 684-7573

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Silver
CASRN -- 7440-22-4

Not available at this time.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Silver
CASRN -- 7440-22-4
Last Revised -- 06/01/89

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk

is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Silver >>>

II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- D; not classified as to human carcinogenicity

Basis -- In animals, local sarcomas have been induced after implantation of foils and discs of silver. However, the interpretation of these findings has been questioned due to the phenomenon of solid-state carcinogenesis in which even insoluble solids such as plastic have been shown to result in local fibrosarcomas.

<<< Silver >>>

II.A.2. HUMAN CARCINOGENICITY DATA

No evidence of cancer in humans has been reported despite frequent therapeutic use of the compound over the years.

<<< Silver >>>

II.A.3. ANIMAL CARCINOGENICITY DATA

Inadequate. Local sarcomas have been induced after subcutaneous (s.c.) implantation of foils and discs of silver and other noble metals. Furst (1979, 1981), however, cited studies showing that even insoluble solids such as smooth ivory and plastic result in local fibrosarcomas and that tin when crumbled will not. He concluded that i.p. and s.c. implants are invalid as indicators of carcinogenicity because a phenomenon called solid-state carcinogenesis may complicate the interpretation of the cause of these tumors. It is difficult to interpret these implantation site tumors in laboratory animals in terms of exposure to humans via ingestion. Within these constraints there are two studies given below in which silver per se appeared to induce no carcinogenic response.

Schmahl and Steinhoff (1960) reported, in a study of silver and of gold, that colloidal silver injected both i.v. and s.c. into rats resulted in tumors in 8 of 26 rats which survived longer than 14 months. In 6 of the 8, the tumor was at the site of the s.c. injection. In about 700 untreated rats the rate of spontaneous tumor formation of any site was 1 to 3%. No vehicle control was reported.

Furst and Schlauder (1977) evaluated silver and gold for carcinogenicity in a study designed to avoid solid-state carcinogenesis. Metal powder was suspended in trioctanoin and injected monthly, i.m., into 50 male and female Fischer 344 rats per group. The dose was 5 mg each for 5 treatments and 10 mg each for 5 more treatments for a total dose of 75 mg silver. The treatment regimen included a vehicle control (a reportedly inert material), and cadmium as a positive control. Injection site sarcomas were found only in vehicle control (1/50), gold (1/50) and cadmium (30/50); no tumors (0/50) appeared at the site of injection in the silver-treated animals. A complete necropsy was

performed on all animals. The authors mentioned the existence of spontaneous tumors in Fischer 344 rats, but reported only injection site tumors. They concluded that finely divided silver powder injected i.m. does not induce cancer.

<<< Silver >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Further support for the lack of silver's ability to induce or promote cancer stems from the finding that, despite long standing and frequent therapeutic usage in humans, there are no reports of cancer associated with silver. In a recent Proceedings of a Workshop/Conference on the Role of Metals in Carcinogenesis (1981) containing 24 articles on animal bioassays, epidemiology, biochemistry, mutagenicity, and enhancement and inhibition of carcinogenesis, silver was not included as a metal of carcinogenic concern.

No evidence of the mutagenicity of silver was shown in two available studies. Demerec et al. (1951) studied silver nitrate for the possible induction of back-mutations from streptomycin dependence to nondependence in Escherichia coli. Silver nitrate was considered nonmutagenic in this assay. Nishioka (1975) screened silver chloride with other chemicals for mutagenic effects using a method called the rec-assay. Silver chloride was considered nonmutagenic in this assay.

----------<<< Silver >>>----------

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not available.

----------<<< Silver >>>----------

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

----------<<< Silver >>>----------

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

____II.D.1. EPA DOCUMENTATION

U.S. EPA. 1988. Drinking Water Criteria Document for Silver. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. ECAO-CIN-026. Final Draft.

<<< Silver >>>

____II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The 1988 Drinking Water Criteria Document for Silver has received Agency

review.

Agency Work Group Review: 09/22/88

Verification Date: 09/22/88

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

W. Bruce Peirano / ORD -- (513)569-7540 / FTS 684-7540

Julie Du / ODW -- (202)382-7583 / FTS 382-7583

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

__III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Silver
CASRN -- 7440-22-4

Not available at this time.

__III.B. OTHER ASSESSMENTS

Substance Name -- Silver
CASRN -- 7440-22-4

Content to be determined.

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Silver
CASRN -- 7440-22-4
Last Revised -- 03/01/88

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve

enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

<<< Silver >>>

__IV.A. CLEAN AIR ACT (CAA)

No data available

----------<<< Silver >>>----------

__IV.B. SAFE DRINKING WATER ACT (SDWA)

___IV.B.1. MAXIMUM CONTAMINANT LEVEL (MCL) for Drinking Water

Value (status) -- 0.05 mg/L (1980)

Considers technological or economic feasibility? -- NO

Discussion --

Reference -- 45 FR 57332 (08/27/80)

EPA Contact -- James Murphy / Criteria and Standards Division, ODW / (202)382-7571 / FTS 382-7571; or Drinking Water Hotline / (800)426-4791

----------<<< Silver >>>----------

__IV.C. CLEAN WATER ACT (CWA)

___IV.C.1. AMBIENT WATER QUALITY CRITERIA, Human Health

Water and Fish Consumption: 5E+1 ug/L

Fish Consumption Only: None

Considers technological or economic feasibility? -- NO

Discussion -- This value is the same as the drinking water standard and approximates a safe level assuming consumption of contaminated organisms and water.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division, OWRS (202)475-7315 / FTS 475-7315

<<< Silver >>>

___IV.C.2. AMBIENT WATER QUALITY CRITERIA, Aquatic Organisms

Freshwater:

Acute -- Varies with hardness
Chronic LEC -- 1.2E-1 ug/L

Marine:

Acute -- 2.3E+0 ug/L
Chronic -- None

Considers technological or economic feasibility? -- NO

Discussion -- The values that are indicated as "LEC" are not criteria, but are the lowest effect levels found in the literature. LECs are given when the minimum data required to derive water quality criteria are not available. The freshwater acute criterion varies with water hardness. For freshwater aquatic life the concentration (in ug/L) of total recoverable silver should not exceed the numerical value given by the equation "e**(1.72 [ln (hardness)]-6.52)" (** indicates exponentiation; hardness is in mg/L). For example, at a hardness of 50 mg/L, the acute WQC would be 1.2 and, at a hardness of 100 mg/L, the criterion would be 4.1 mg/L.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

----------<<< Silver >>>----------

__IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

No data available

----------<<< Silver >>>----------

__IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

----------<<< Silver >>>----------

__IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

___IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

----------<<< Silver >>>----------

IV.G. SUPERFUND (CERCLA)

IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) -- 1000 pounds (Final, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- The final RQ is based on chronic toxicity. RQ assignments based on chronic toxicity reflect two primary attributes of the hazardous substance, the minimum effective dose (MED) levels for chronic exposure (mg/day for 70 kg person) and the type of effect (liver necrosis, teratogenicity, etc). A composite score is determined from an evaluation of these two attributes. Silver was determined to have a composite score of between 6 and 20, corresponding to a chronic toxicity RQ of 1000 pounds.

Reference -- 50 FR 13456 (04/04/85)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

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V. SUPPLEMENTARY DATA

Substance Name -- Silver
CASRN -- 7440-22-4

Not available at this time.

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VI. BIBLIOGRAPHY

Substance Name -- Silver
CASRN -- 7440-22-4
Last Revised -- 08/01/89

VI.A. ORAL RfD REFERENCES

Blumberg, H. and T.N. Carey. 1934. Argyremia: Detection of unsuspected and obscure argyria by the spectrographic demonstration of high blood silver. J. Am. Med. Assoc. 103(20): 1521-1524.

East, B.W., K. Boddy, E.D. Williams, D. MacIntyre and A.L.C. McLay. 1980. Silver retention, total body silver and tissue silver concentrations in argyria associated with exposure to an anti-smoking remedy containing silver acetate. Clin. Exp. Dermatol. 5: 305-311.

Gaul, L.E. and A.H. Staud. 1935. Clinical spectroscopy. Seventy cases of

generalized argyrosis following organic and colloidal silver medication, including a biospectrometric analysis of ten cases. J. Am. Med. Assoc. 104(16): 1387-1390.

----------<<< Silver >>>----------

__VI.B. INHALATION RfD REFERENCES

None

----------<<< Silver >>>----------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Demerec, M., G. Bertani and J. Flint. 1951. A survey of chemicals for mutagenic action on E. coli. Am. Nat. 85(821): 119-136.

Furst, A. 1979. Problems in metal carcinogenesis. In: Trace Metals in Health and Disease, N. Kharasch, Ed. Raven Press, New York. p. 83-92.

Furst, A. 1981. Bioassay of metals for carcinogenesis: Whole animals. Environ. Health Perspect. 40: 83-92.

Furst, A. and M.C. Schlauder. 1977. Inactivity of two noble metals as carcinogens. J. Environ. Pathol. Toxicol. 1: 51-57.

Nishioka, H. 1975. Mutagenic activities of metal compounds in bacteria. Mutat. Res. 31: 185-189.

Proceedings of a Workshop/Conference on the Role of Metals in Carcinogenesis. 1981. Environ. Health Perspect. 40: 252.

Schmahl, D. and D. Steinhoff. 1960. Versuche zur Krebserzeugung mit kolloidalen Silber-und Goldlosungen an Ratten. Z. Krebsforsch. 63: 586-591.

U.S. EPA. 1988. Drinking Water Criteria Document for Silver. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. ECAO-CIN-026. Final Draft.

----------<<< Silver >>>----------

__VI.D. DRINKING WATER HA REFERENCES

None

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SYNONYMS

Substance Name -- Silver
CASRN -- 7440-22-4

7440-22-4
ARGENTUM CREDE
COLLARGOL
Silver

Zinc and Compounds; CASRN 7440-66-6 (02/01/91)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR Zinc and Compounds

File On-Line 02/01/91

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	pending	
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	02/01/91
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	no data	
Supplementary Data (V.)	no data	

I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Zinc and Compounds
CASRN -- 7440-66-6

A risk assessment for this substance/agent is under review by an EPA work group.

I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Zinc and Compounds
CASRN -- 7440-66-6

Not available at this time.

II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Zinc and Compounds
CASRN -- 7440-66-6
Last Revised -- 02/01/91

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Zinc and Compounds >>>

II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- D; not classifiable as to human carcinogenicity

Basis -- Based on inadequate evidence in humans and animals.

<<< Zinc and Compounds >>>

II.A.2. HUMAN CARCINOGENICITY DATA

Inadequate. There are no reports on the possible carcinogenicity of zinc and compounds per se in humans. Case studies have been used to evaluate the effects of zinc administered for therapeutic reasons. There are reports which compare zinc levels in normal and cancerous tissue. Studies of occupational exposure to zinc compounds have also been conducted, but have limited value because they do not correlate exposure with cancer risk.

Case reports of chronic therapeutic exposure for approximately 2 years of two patients, a 59-year-old female and a 26-year-old homozygous sickle-cell male, to 100-150 mg/day zinc as zinc sulfate or zinc acetate, respectively, have reported a profound anemia associated with hypoceruloplasminemia and hypocupremia (Porter et al., 1977; Prasad et al., 1978). The conditions were corrected by copper supplementation and, in one case, withdrawal of zinc.

Habib et al. (1976) reported that average zinc concentrations in normal and hypertrophic prostate tissues were similar, approximately 6.8 umol/g, but the average zinc concentration was lower in carcinomatous prostate tissues (2.6 umol/g). These tissue samples were obtained as follows: normal prostate tissues were obtained at autopsy from 9 men 25-58 years old (average age 36); and both hyperplastic and carcinomatous prostate tissues were obtained from the biopsies of 23 men 58-87 years old (average age 70) and from 9 men 64-91 years old (average age 73), respectively. Several other studies have also shown lower average zinc concentrations in cancerous vs. normal or hypotrophic prostate tissue (U.S. EPA, 1987). NRC (1978) and U.S. EPA (1987) have reviewed other studies which have noted both high and low zinc levels in other cancerous and noncancerous tissues with no definite pattern. From these studies it could not be concluded whether zinc was a carcinogen.

Several occupational studies have been conducted on workers exposed to zinc compounds (Batchelor et al., 1926; Chmielewski et al., 1974a,b; Bobrishchev-Pushkin et al., 1977). No increase in the incidence of cancer was noted; however, the studies were designed to evaluate other endpoints and did not specifically address cancer. Other symptoms such as slight leukocytosis, occurrences of metal fume fever, respiratory disease and hypocalcemia were some of the findings noted in exposed workers. Batchelor et al. (1926) extensively investigated workers exposed to zinc in a smelter. A total of 24 workers whose exposure ranged from 2-35.5 years were selected. In most work areas the mean zinc concentrations were generally below 35 mg/cu.m, except in the zinc dust plant where concentrations of up to 130 mg/cu.m were measured. The average level of zinc in whole blood of the 24 exposed workers was 458 ug/100 mL, compared with 387 ug/100 mL in 10 control measurements. No information was given about the control subjects. Klucik and Koprda (1979) found that exposure levels to zinc oxide dust in a zinc oxide factory were on average 0.5 mg/cu.m for zinc melters and 2.44-7.15 mg/cu.m for zinc oxide packers; it was not indicated how these values were obtained. Chmielewski et al. (1974a,b) examined a group of workers who were exposed to zinc oxide in a shipyard; this included 20 ship smiths, 20 electric welders, 20 ship's pipeline fitters, and 20 zincifying workers. High concentrations of zinc oxide were found at the stands of the electric welders, who worked in containers (maximum 58 mg/cu.m, mean 18 mg/cu.m), and the ship smiths, who worked in a superstructure (maximum 50 mg/cu.m, mean 12 mg/cu.m). These workers were also exposed to other hazardous compounds, such as nitrogen oxides. Bobrishchev-Pushkin et al. (1977) studied 1018 workers in the casting shops of three copper alloy production facilities in the USSR. Four hundred and fifty-one workers from the rolling shops were used as controls. The average level of zinc oxide exposure in the casting shop was 2.1 mg/cu.m (range of 0.2-5.1 mg/cu.m), well below the USSR's maximally allowable concentration of 6 mg/cu.m. Workers were also exposed to other metals such as copper, lead and nickel.

<<< Zinc and Compounds >>>

II.A.3. ANIMAL CARCINOGENICITY DATA

Inadequate. In a 1-year study, an unspecified number of newborn Chester Beatty stock mice (sex not reported) were administered 0, 1000, or 5000 ppm

zinc (approximately 0, 170, or 850 mg/kg/day) as zinc sulfate in drinking water (Walters and Roe, 1965). A separate group of mice received zinc oleate in the diet at an initial dose of 5000 ppm zinc; this dose was reduced to 2500 ppm after 3 months and to 1250 ppm after an additional 3 months because of mortality due to anemia. An epidemic of ectromelia caused the deaths of several mice during the first 8 weeks; consequently, additional control and test-diet groups were established. There was no difference in body weight gain between control and treated groups, except the dietary zinc group which became anemic. Survival was not reported in treated compared with control groups.

An apparent increase in the incidence of hepatomas was observed in treated mice surviving for 45 weeks or longer relative to controls (original and replacement mice pooled). The hepatoma incidence in the control, low-dose drinking water, high-dose drinking water, and test-diet group was 3/24 (12.5%), 3/28 (10.7%), 3/22 (13.6%), and 7/23 (30.4%), respectively. Incidence of malignant lymphoma in the control, low-dose drinking water, high-dose drinking water, and test-diet groups was 3/24 (12.5%), 4/28 (14.3%), 2/22 (9%), and 2/23 (8.7%), respectively. Incidence of lung adenoma in the control, low-dose drinking water, high-dose drinking water, and test-diet groups was 10/24 (41.7%), 9/28 (32.1%), 5/22 (22.7%), and 9/23 (39.1%), respectively. None of these were significantly elevated in a statistical analysis of this data performed by the EPA. In a 14-month study conducted with 150 C3H mice (sex not reported), administration of 500 mg/L zinc sulfate (approximately 100 mg/kg/day) in the drinking water resulted in hypertrophy of the adrenal cortex and pancreatic islets (Aughey et al., 1977). No tumors were noted; however, only the adrenal, pancreas and adenohypohysis were examined. Accurate consumption data could not be obtained due to spillage during drinking. No instances of adrenal or pancreatic hypertrophy were seen in a control group (number of animals not stated) that received only distilled water.

After an intratesticular injection of zinc, Guthrie observed seasonally-related testicular tumors in fowl (Guthrie, 1964) but no tumors in rats (Guthrie, 1956). Guthrie (1964) administered zinc chloride, zinc acetate or zinc stearate to groups of white leghorn chickens by intratesticular injection (approximately 0.01 g/injection); groups of chickens were sacrificed from 3 weeks to 11 months. Eight of the 111 chickens injected with zinc chloride in January and February developed testicular testoma, while none of the 48 chickens injected with zinc chloride in March developed tumors. None of the 36 chickens injected with zinc acetate in March and none of the 14 chickens injected with zinc stearate in January and February developed tumors; no conclusions about the carcinogenicity of these two compounds could be made because an insufficient number of chickens were tested. No control group was described.

Guthrie injected 0.15-0.20 mL of 10% zinc sulfate into the testis of nineteen 4-month-old rats and 0.15 mL of 5% zinc chloride into the testis of twenty-nine 3-month-old rats (strain not specified) (Guthrie 1956). No testicular tumors were observed in either group at sacrifice 15 months after injection. No controls were described. Riviere et al. (1959) injected 5% zinc chloride in distilled water into the testicles of 100 Wistar rats. The rats were subdivided into several groups; some rats were unilaterally castrated and some rats received an injection of 200 units serum gonadotrophin and a subcutaneous implantation of a 25 mg pellet of distilbene or 100 mg testosterone. The number of rats in each of the four groups (unilateral castration +/- hormone treatment and untreated +/- hormone treatment was not stated. No control group was described. Testicular tumors (including interstitial tumors, a seminoma and an embryoma) became apparent 15 months after inoculation (tumor incidence not specified). There are no specific data

on the effects of hormones in this experiment.

Halme (1961) exposed tumor-resistant and tumor-susceptible strains of mice to zinc in drinking water. In a 3-year, five-generation study, zinc chloride was added to the water of tumor-resistant mice (strain not specified); the groups received 0, 10, 20, 50, 100, or 200 mg Zn/L. The spontaneous tumor frequency for this strain of mice was 0.0004%. The tumor frequencies in the generations were: F0=0.8%, F1=3.5%, F1 and F2=7.6% and F3 and F4=25.7%. Most of the tumors occurred in the 10 and 20 mg Zn dose groups. No statistical analyses and no individual tumor-type data were reported. In the tumor-susceptible mice, strains C3H and A/Sn received 10-29 mg Zn/L in their drinking water for 2 years; 33/76 tumors were observed in the C3H strain (31 in females) and 24/74 tumors were observed in the A/Sn strain (20 in females). Most of the tumors were adenocarcinomas. The numbers of specific tumor types were not reported. The tumor frequencies (43.4% for C3H and 32.4% for A/Sn both sexes combined) were higher than the spontaneous frequency (15% for each strain), although no statistical analyses were reported.

<<< Zinc and Compounds >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

In a short-term, in vivo assay, Stoner et al. (1976) injected strain A/Strong mice (20/sex/dose) intraperitoneally with zinc acetate 3 times/week for a total of 24 injections (total doses were 72, 180, or 360 mg/kg). Controls (20/sex/group) consisted of an untreated group, a vehicle control group administered 24 injections of saline and a positive control group administered a single injection of urethan (20 mg/mouse). Mice were sacrificed 30 weeks after the first injection; survival was comparable for all groups. There was no increase in number of lung tumors per mouse in treated animals relative to the pooled controls. While four thymomas were observed in zinc acetate-treated groups and none in controls, the occurrence of these tumors was not statistically significantly elevated.

Urine samples from subjects occupationally exposed in the rubber industry to a variety of compounds, including zinc oxide, were not found to be mutagenic in the microtitre fluctuation assay with Salmonella typhimurium strains TA1535, TA98 and TA100 (Crebelli et al., 1985).

The results of short-term genotoxicity assays for zinc are equivocal. Zinc acetate and/or zinc 2,4-pentanedione have been analyzed in four short-term mutagenicity assays (Thompson et al., 1989). In the Salmonella assay (with or without hepatic homogenates), zinc acetate was not mutagenic over a dose range of 50-7200 ug/plate but zinc 2,4-pentanedione was mutagenic to strains TA1538 and TA98 at 400 ug/plate. The addition of hepatic homogenates diminished this response in a dose-dependent manner. In the mouse lymphoma assay, zinc acetate gave a dose-dependent positive response with or without metabolic activation; the mutation frequency doubled at 10 ug/mL. In the CHO in vitro cytogenetic assay, zinc acetate gave a dose-dependent positive response with or without metabolic activation, but the presence of hepatic homogenates decreased the clastogenic effect. Neither zinc acetate nor zinc 2,4-pentanedione were positive in the unscheduled DNA synthesis assay in rat hepatocytes over a dose range of 10-1000 ug/mL.

Zinc chloride is reported to be positive in the Salmonella assay (Kalinina et al., 1977), negative in the mouse lymphoma assay (Amacher and Paillet, 1980), and a weak clastogen in cultured human lymphocytes (Deknudt and Deminatti, 1978). Zinc sulfate is reported to be not mutagenic in the Salmonella assay (Gocke et al., 1981), and zinc acetate is reported to not induce chromosomal abberations in cultured human lymphocytes (Gasiorek and

Bauchinger, 1981). Crebelli et al. (1985) found zinc oxide (99% purity) (1000-5000 ug/plate) to be not mutagenic for Salmonella in the reversion assay.

Responses in mutagenicity assays are thought to depend on the form (e.g., inorganic or organic salt) of the zinc tested. For example, inorganic salts tend to dissociate and the zinc becomes bound with culture media constituents. Salts that dissociate less readily tend to be transported into the cell and are postulated to cause a positive response (Thompson et al., 1989). Zinc is an essential trace element involved in numerous biological functions including growth, taste and spermatogenesis. It is a cofactor for several enzymes such as those involved in the metabolism of proteins and nucleic acids. Zinc may be a modifier of the carcinogenic response; zinc deficiency or excessively high levels of zinc may enhance susceptibility to carcinogenesis, whereas supplementation with low to moderate levels of zinc may offer protection (Woo et al., 1988). Zinc deficiency enhanced carcinomas of the esophagus induced by methylbenzylnitrosoamine (Fong et al., 1978) but retarded the development of cancer of the oral cavity induced by 4-nitroquinoline-N-oxide (Wallenius et al., 1979). In a study that examined both zinc deficiency and supplementation, Mathur (1979) found that animals with a deficient diet (5.9 mg/kg) and animals diet supplemented with excessively high levels of zinc in the diet (200-260 mg/kg) had fully developed carcinomas of the palatial mucosa. While the rats were on the specific diets, the palatial mucosa was painted with 4 nitroquinoline 3 times/week for 20 weeks. In the zinc deficient group 2/25 rats developed cancer of the palatial mucosa; 2/25 rats in the excessive zinc group also developed this form of cancer. Animals supplemented with moderate levels of zinc in the diet (50 mg/kg) developed only moderate dysplasia. Thus, zinc's modifying effect on carcinogenesis may be dose-dependent.

----------<<< Zinc and Compounds >>>----------

II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

None.

----------<<< Zinc and Compounds >>>----------

II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

None.

----------<<< Zinc and Compounds >>>----------

II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

II.D.1. EPA DOCUMENTATION

U.S. EPA. 1980. Ambient Water Quality Criteria for Zinc. Prepared by the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-079.

U.S. EPA. 1984. Health Effects Assessment for Zinc (and Compounds). Prepared by the Office of Health and Environmental Assessment, Environmental

Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1987. Summary Review of the Health Effects Associated with Zinc and Zinc Oxide. Health Issue Assessment. Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA/600/8-87/022F.

U.S. EPA. 1988. Ambient Water Quality Criteria Document Addendum for Zinc. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC.

<<< Zinc and Compounds >>>

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The 1984 Health Effects Assessment for Zinc (and compounds), the 1987 Health Issue Assessment and the 1980 abd 1988 Ambient Water Quality Criteria Documents have received Office of Health Effects Assessment review.

Agency Work Group Review: 11/08/89, 06/15/90

Verification Date: 06/15/90

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Rita S. Schoeny / ORD -- (513)569-7544 / FTS 684-7544

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

__III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Zinc and Compounds
CASRN -- 7440-66-6

Not available at this time.

__III.B. OTHER ASSESSMENTS

Substance Name -- Zinc and Compounds
CASRN -- 7440-66-6

Content to be determined.

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Zinc and Compounds
CASRN -- 7440-66-6

Not available at this time.

_V. SUPPLEMENTARY DATA

Substance Name -- Zinc and Compounds
CASRN -- 7440-66-6

Not available at this time.

_VI. BIBLIOGRAPHY

Substance Name -- Zinc and Compounds
CASRN -- 7440-66-6
Last Revised -- 02/01/91

__VI.A. ORAL RfD REFERENCES

None

----------<<< Zinc and Compounds >>>----------

__VI.B. INHALATION RfC REFERENCES

None

----------<<< Zinc and Compounds >>>----------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Amacher, D.E. and S.C. Paillet. 1980. Induction of trifluorothymidine-resistant mutants by metal ions in L5178Y/TK+/- cells. Mutat. Res. 78: 279-288.

Aughey, E., L. Grant, B.L. Furman and W.F. Dryden. 1977. The effects of oral zinc supplementation in the mouse. J. Comp. Pathol. 87:1-14.

Batchelor, R.P., J.W. Fehnel, R.M. Thomson and K.R. Drinker. 1926. A clinical and laboratory investigation of the effect of metallic zinc, of zinc oxide and of zinc sulphide upon the health of workmen. J. Ind. Hyg. 8: 322-363. (Summarized in U.S. EPA, 1987)

Bobrishchev-Pushkin, D.M., A.A. Orlova, L.A. Naumova et al. 1977. Occupationl hygiene and health status of workers engaged in production of copper alloys. Gig. Tr. Prof. Zabol. (8): 10-14. (Eng. trans.)

Chmielewski, J., B. Jaremin, C. Bartnicki and R. Konieczka. 1974a. Evaluation of occupational exposure to zinc oxide in the marine production shipyard: I. Examination of the working environment and the stands under exposure. Biul. Inst. Med. Morsk. Gdansk. 25(1): 43-51. (Summarized in U.S. EPA, 1987)

Chmielewski, J., B. Jaremin, C. Bartnicki and R. Konieczka. 1974b. Evaluation of occupational exposure to zinc oxide in the marine production shipyard: II. Examination of the state of health of the workers exposed to zinc oxide. Biul. Inst. Med. Morsk. Gdansk. 25(1): 53-65. (Summarized in U.S. EPA, 1987)

Crebelli, R., A. Paoletti, E. Falcone, G. Aquilina, G. Fabri and A. Carere. 1985. Mutagenicity studies in a tyre plant: In vitro activity of workers' urinary concentrates and raw materials. Br. J. Ind. Med. 42: 481-487.

Deknudt, G. and M. Deminatti. 1978. Chromosome studies in human lymphocytes after in vitro exposure to metal salts. Toxicology. 10: 67-75.

Fong, L.Y.Y., A. Sivak and P.M. Newberne. 1978. Zinc deficiency and methylbenzylnitrosoamine-induced esophageal cancer in rats. J. Natl. Cancer Inst. 61: 145-150.

Gasiorek, K. and M. Bauchinger. 1981. Chromosome changes in human lymphocytes after separate and combined treatment with divalent salts of lead, cadmium, and zinc. Environ. Mutagen. 3: 513-518.

Gocke, E., M.T. King, K. Echardt and D. Wild. 1981. Mutagenicity of cosmetics ingredients licensed by the European Communities. Mutat. Res. 90: 91-109.

Guthrie, J. 1956. Attempts to produce seminomata in the albino rat by inoculation of hydrocarbons and other carcinogens into normally situated and ectopic testes. Br. J. Cancer. 10: 134-144.

Guthrie, J. 1964. Observations on the zinc induced testicular teratomas of fowl. Br. J. Cancer. 18: 130-142.

Habib, F.K., G.L. Hammond, I.R. Lee et al. 1976. Metal-androgen interrelationships in carcinoma and hyperplasia of the human prostate. J. Endocr. 71: 133-141.

Halme, E. 1961. On the carcinogenic effect of drinking water containing zinc. Vitalstoffe. 6: 59-66. (Ger.) (Eng. trans.)

Kalinina, L.M., G.H. Polukhina and L.I. Lukasheva. 1977. Salmonella Typhimurium - Test system for indication of mutagenic activity of environmental hazards. I. Detection of mutagenic effect of heavy metal salts using in vivo and in vitro assays without metabolic activation. Genetika. 13: 1089-1092.

Klucik, I. and J. Koprda. 1979. Hypocalcaemia in subjects after long-term exposure to zinc oxide. Prac. Lek. 31(6): 234-237. (Summarized in U.S. EPA, 1987)

Mathur, A., K. Wallenius, and M. Abdulla. 1979. Influence of zinc on onset and progression of oral carcinogenesis in rats. Acta Odontologica Scand. 37: 377-384. (Cited in U.S. EPA, 1980)

NRC (National Research Council). 1978. Zinc. University Park Press, Baltimore MD. p. 258-261.

Porter, K.G., D. McMaster, M.E. Elmes and A.H.G. Love. 1977. Anemia and low serum-copper during zinc therapy. Lancet. p. 744.

Prasad, A.S., G.J. Brewer, E.B. Schoomaker and P. Rabbani. 1978. Hypocupremia induced by zinc therapy in adults. J. Am. Med. Assoc. 240(20): 2166-2168.

Riviere, M.R., I. Chouroulinkov and M. Guerin. 1959. Testicular tumors in the rat after injection of zinc chloride. C.r. hebd. Seanc. Acad. Sci., Paris. 249: 2649-2651. (Fre.) (Eng. trans.)

Stoner, G.D., M.B. Shimkin, M.C. Troxell, T.L. Thompson and L.S. Terry. 1976. Test for carcinogenicity of metallic compounds by the pulmonary tumor response in strain A mice. Cancer Res. 36(5): 1744-1747.

Thompson, E.D., J.A. McDermott, T.B. Zerkle, J.A. Skare, B.L.B. Evans and D.B. Cody. 1989. Genotoxicity of zinc in 4 short-term mutagenicity assays. Mutat. Res. 223: 267-272.

U.S. EPA. 1980. Ambient Water Quality Criteria for Zinc. Prepared by the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-079.

U.S. EPA. 1984. Health Effects Assessment for Zinc (and Compounds). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1987. Summary Review of the Health Effects Associated with Zinc and Zinc Oxide. Health Issue Assessment. Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA/600/8-87/022F.

U.S. EPA. 1988. Ambient Water Quality Criteria Document Addendum for Zinc. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC.

Wallenius, K., A. Mathur and M. Abdulla. 1979. Effect of different levels of dietary zinc on development of chemically induced oral cancer in rats. Int. J. Oral Surg. 8: 56-62.

Walters, M. and F.J.C. Roe. 1965. A study of the effects of zinc and tin administered orally to mice over a prolonged period. Food Cosmet. Toxicol. 3: 271-276.

Woo, Y.T., D.Y. Lai, J.C. Arcos and M.F. Argus. 1988. Chemical Induction of Cancer: Structural Bases and Biological Mechanisms. Vol. IIIC, Natural, Metal, Fiber and Macromolecular Carcinogens. Academic Press, San Diego. p. 488-489.
In preparation
Not available at this time

None

----------<<< Zinc and Compounds >>>----------

VI.D. DRINKING WATER HA REFERENCES

None

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SYNONYMS

Substance Name -- Zinc and Compounds
CASRN -- 7440-66-6
Last Revised -- 02/01/91

7440-66-6
Zinc
Asarco L 15
Blue powder
Cinc [Spanish]
EMANAY ZINC DUST
GRANULAR ZINC
HSDB 1344
JASAD
Lead refinery vacuum zinc
Merrillite
UN 1436
Zinc
ZINC DUST
ZINC POWDER
ZINC, ashes
ZINC, powder or dust, non-pyrophoric
ZINC, powder or dust, pyrophoric

APPENDIX D

SUMMARY OF RECENT ANALYTICAL RESULTS FOR SEDIMENT FROM WASTEWATER TREATMENT PONDS

APPENDIX D

SUMMARY OF ANALYTICAL RESULTS FOR SEDIMENT FROM WASTEWATER TREATMENT PONDS

RMI SODIUM FACILITY ASHTABULA, OHIO

Parameter	Detection Limits	Regulatory Limits	0874[a] Pond #1 Sediment	3922[b] Pond Filtercake
TCLP Metals[c]				
Arsenic	0.005	5.0	BMDL[d]	BMDL
Barium	0.20	100	0.49	1.19
Cadmium	0.010	1.0	BMDL	BMDL
Chromium	0.05	5.0	0.07	0.10
Lead	0.10	5.0	BMDL	BMDL
Mercury	0.002	0.2	0.008	BMDL
Selenium	0.005	1.0	BMDL	BMDL
Silver	0.02	5.0	0.03	0.07
Original pH (units)	NA[e]	NA	--	11.6
Final pH (units)	NA	NA	--	10.4
TCLP Organics[c]				
Carbon Tetrachloride	0.002	0.5	--	BMDL
Chlorobenzene	0.002	100	--	BMDL
Chloroform	0.002	6.0	--	0.011[f]
1,4-Dichlorobenzene	0.002	7.5	--	BMDL
1,2-Dichloroethane	0.002	0.5	--	BMDL
1,1-Dichloroethylene	0.002	0.7	--	BMDL
MEK	0.020	200	--	BMDL
Tetrachloroethylene	0.002	0.7	--	BMDL
Trichloroethylene	0.002	0.5	--	BMDL
Vinyl Chloride	0.002	0.2	--	BMDL
Benzene	0.002	0.5	--	BMDL
o-Cresol	0.002	200	--	BMDL
m-cresol	0.002	200	--	BMDL
p-cresol	0.002	200	--	BMDL
Cresol	0.002	200	--	BMDL
2,4-Dinitrotoluene	0.002	0.13	--	BMDL
Hexachlorobenzene	0.002	0.13	--	BMDL
Hexachlorobutadiene	0.002	0.5	--	BMDL
Hexachloroethane	0.002	3.0	--	BMDL
Nitrobenzene	0.002	2.0	--	BMDL
Pentachlorophenol	0.002	100	--	BMDL
Pyridine	0.002	5.0	--	BMDL
2,4,5-Trichlorophenol	0.002	400	--	BMDL
2,4,6-Trichlorophenol	0.002	2.0	--	BMDL

APPENDIX D (Continued)

SUMMARY OF ANALYTICAL RESULTS FOR SEDIMENT FROM WASTEWATER TREATMENT PONDS

RMI SODIUM FACILITY ASHTABULA, OHIO

Parameter	Detection Limits	Regulatory Limits	0874[a] Pond #1 Sediment	3922[b] Pond Filtercake
PCBs By USEPA Method 8080[g,h]				
PCB-1016	1.0	--	--	BMDL
PCB-1221	1.0	--	--	BMDL
PCB-1232	1.0	--	--	BMDL
PCB-1242	1.0	--	--	BMDL
PCB-1248	1.0	--	--	BMDL
PCB-1254	1.0	--	--	BMDL
PCB-1260	1.0	--	--	BMDL
Wet Chemistry[g]				
Total Petroleum Hydrocarbons	25	--	--	BMDL
Corrosivity (pH) (units)	NA	--	--	12.3
Ignitability-Flashpoint (DEG-F)	NA	--	--	>212

[a]Date Sampled: January 25, 1991.
[b]Date Sampled: June 26, 1991.
[c]All results expressed in milligrams/liter (mg/L) unless otherwise noted.
[d]BMDL = Below Method Detection Limit.
[e]NA = Not Applicable.
[f]Chloroform concentration of 0.009 mg/L detected in TCLP Blank.
[g]All results expressed in milligrams/kilogram (mg/kg; wet) unless otherwise noted.
[h]Other matrix present in the sample.